Quarterly Progress Reports

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Neural Prosthetic control

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Contents

This Quarterly Report is organized into five sections. First there is a summary of the overall objectives of the contract. In the subsequent three sections we describe the goals and activities of the three main components of the project: Array development, development of decoding algorithms, and development of interfaces. Each section has, at its end, a description of the progress made during the current quarter on that phase of the project. Lastly, we describe project goals for the upcoming quarter.

1. Introduction

A number of neurological disorders, such as spinal cord injury, MD and ALS result in the inability to make voluntary movements. A major reason for paralysis in these disorders is a disconnection of the signal from a normal brain from the spinal cord or muscles. Devices that can detect and decode motor commands have the potential to restore voluntary actions in these individuals. The purpose of this project is to demonstrate the ability to use neural signals to control real world devices in monkeys; such devices can ultimately serve as prosthetic aids for paralyzed individuals.

Control signals for prosthetic devices can be derived from a number of sources, including the eyes, muscles, and EEG. These signals are, however, rather limited in the number of dimensions they can control. Going beyond a one dimensional control signal is difficult and often interferes with natural behavior. For example, two dimensional EEG control requires full attention to control without distraction (such as gaze shifts). By contrast, populations of neurons appear to contain rich signals, potentially able to control multiple dimensions. However, chronic recording of multiple neurons in primates has been technically challenging, the ability to decode neural activity into meaningful control signals is poorly understood and the ability to control devices using such signals is not developed.

The overall goal of this work is to develop a means to bring a robotic arm under near real time neural control using a multineuron signal derived from a recording device that is chronically implanted in a macaque monkey motor cortex. This project has three specific objectives. The **first objective** is to develop and test technologically advanced neural recording devices in a non-human primate model. This work examines the stability, efficiency and biocompatibility of electrode arrays and the suitability of the primary motor cortex as a sight to obtain neural recordings. Once recorded, neural activity must be decoded into meaningful control signals. The optimal methods for such decoding are not obvious. A **second objective** of the project is to examine various decoding methods and evaluate their ability to be useful control signals. This requires mathematical tools and signal processing that reconstructs intended actions from abstract, neurally based motor commands generated in the cortex. This aspect of the project involves fundamental motor control questions, such as what coordinate system is used to encode voluntary actions. **A third objective** of this project is to show that such signals can be used to control devices such as a robotic arm or a computer interface. These devices serve as a proxy for the lost limb and can be used to recreate useful actions like those intended for the arm. Successful completion of these goals would suggest that this approach could be used to restore movement in paralyzed humans.

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2. . Summary of Achievements this Quarter. We began the project. A new technician, Lauren Lennox was identified, hired and trained to direct primate training. Monkeys were purchased, delivered, and after their quarantine period were made available for training. Dr. Kenji Nakata, a neurosurgical resident, began assisting in array implantation procedures and in stability assessment. Data from 4 monkeys implanted with arrays before this project was evaluated in the context of the project goal. One monkey was trained and implanted with two arrays and recordings were begun.

3. Array Development

The goal of the array development of this aspect of the project is to identify the optimal properties and implantation procedures for Bionic/Utah electrode arrays to ensure long term, reliable recordings in macaque monkey cortex. This requires monkey training in various behavioral tasks, implantation using various modifications in the surgical procedures and in the array assembly and recording to test the quality and stability of units.

3.1 Behavioral training In order to test for motor related neural activity, monkeys are first operantly conditioned to the various arm movement tasks using juice or water reward. Animals are motivated to perform these tasks by restricting access-time to fluids. During training and recording periods, monkeys are allowed as much fluid as they wish to obtain when they perform the training tasks. Fluids are also supplemented after training sessions and on weekends. as approved by the institutional animal care committee. Training tasks are also support the animals' psychological well being because they provide an additional sources of challenge which is rewarded.

3.1.1 Radial direction task: Monkeys are first operantly conditioned (using juice or water reward) to perform an instructed-delay task consisting of visually-guided planar reaching movements from a central holding position to a radially located target. Animals move a two-joint manipulandum in the horizontal plane to direct a cursor from a central hold position to one of eight possible radially positioned targets (6 cm away from start position) viewed on a computer monitor. Hand position is recorded as the x and y location of the manipulandum using a digitizing tablet, with a sampling rate of 200 Hz. The tangential velocity and acceleration of the hand is computed by numerical differentiation using own custom software. A trial is composed of three epochs: a "hold" period during which time the monkey maintains the cursor at the hold position for 0.5 s, a random 1-1.5 s "instructed delay" period during which the target for the forthcoming action appeared but movement is withheld, and a "go" period initiated by target blinking (mean reaction time ~365 ms). Manipulandum position is monitored using a digitizing tablet sampled at 72 Hz. During this period we trained one monkey (B001) in this task.

3.1.2 Continuous tracking task: This task has been developed by our laboratory for a systems analysis approach to describe neural encoding in MI. It overcomes numerous shortcomings of step tracking tasks: correlation of kinematic variables and nonstationarities in behavioral and neural data. This makes it possible to treat each neural spike as an independent sample from a process with a known distribution, a requirement for many statistical tests and for information theoretic analysis. This task uses the same 2 dimensional device as the direction task except that the stimulus must be tracked in a continuous fashion. We generate a broad distribution of movement stimuli that monkeys must track. Data from this task are used to create the linear filters used to test our ability to reconstruct hand motion from neural data.

Our approach is to have the monkey move its hand (the end point effector) across a two dimensional workspace such that the probability distribution of each kinematic variable is as broad as possible (i.e. the monkey will make a series of motions that will, over time, include all possible velocities, positions, etc., within a plane of movement.) For this task monkeys are trained to track a visual target (2 degree white circle on black background) on a computer screen. The target motion is computer controlled to move in a pseudorandom, experimenter determined fashion. The statistics of the motion of the target, and the resultant tracking motion of the monkey's hand, are chosen in such a way that the entropy (the accepted measure of "broadness") of the distribution of motion is maximized under the constraints imposed by reaction time and biomechanical properties of the arm. In other words, the monkey moves its hand so that we sample from the complete space of possible planar arm movements. We hypothesize that it will be possible to mimic the arm kinematics with a prosthetic device (robot arm) by building a series of decoding filters that defines the relationship between the set of kinematic variables and arm movement. Because we have simultaneously recorded neurons, we can use not only the firing rate of each cell, but also the joint or higher order distribution (e.g. covariance) of neuronal activity to extract information about natural, time-varying movement parameters. During this period we wrote software to run this task and created an interface that communicated data from the behavioral control computer to the data acquisition computer. In addition one monkey was trained to perform this task.

3.1.3. Button box task. During this quarter we began to plan a method to accelerate training by making a button box version of the radial task available while monkeys are in the cage.

3.2 Array Implantation*:* Arrays are implanted in the MI arm representation, medial to the spur of the arcuate sulcus, abutting the central sulcus. The ability to locate arm related neurons using these sulcal landmarks has been 100% successful in our tests. The UEA microelectrode arrays consist of 100, 1.0mm long platinized tip, silicon probes arranged in a square grid on 400μm centers. Impedances between 50-500 kΩ (1 nA, 1kHz sine wave) (Nordhausen et al., 1996). Arrays are wired to connectors contained in a custom designed titanium percutaneous pedestal with using 1 mil gold, Teflon insulated wire (the assembly is custom fabricated for us by BTI). Two extra wires (50.8 μm diameter, Pt-Ir 20%) with approximately 5.0 mm of the terminal insulation removed are inserted subdurally and used as reference and as backup. The bundle of gold wires is coated with silicone elastomer (MDX4-4210, Dow Corning, MI). The back of the array and percutaneous connectors are coated with silicone elastomer to mechanically protect the wires and maintain electrical insulation at the bond pad sites.

The array is inserted rapidly into the cortex using a calibrated, pneumatically propelled mass, and typically, the array is and cortical surface is covered by a Teflon sheet. The dura is then loosely closed and this area is covered by a sheet of Gortex followed by silicon elastomer. Finally the entire region is covered with cranioplast cement which is anchored to the skull through a series of titanium bone screws.

Array implantation procedures initially involved several foreign bodies, which are undesirable if arrays are to be implanted in humans. These include placement of Teflon sheets above and below the dura, addition of silicone elastomere and dental acrylic sealant. Particularly undesirable is the use of acrylic. In consultation with Dr. Gerhard Friehs (neurosurgeon at Brown) we planned new methods of implantation devised to remove the

number of foreign bodies we currently use and to test the importance of keeping the array free of dural attachment. We then tested three different methods of sealing the array in place in one monkey (B164); these arrays were also used to evaluate tissue reactions after 85 days in situ (one additional array in this monkey was in place 141 days). In one of these three implantations we replaced the acrylic seal with a titanium mesh (Timesh) covering, in a second we replaced the bone flap above the array and in the third we used our standard acrylic closure. This monkey was perfused for histological processing and the brain is being prepared with stains to evaluate tissue reaction and the damage done by implantation methods. Timesh was used to replace the acrylic seal in a second array implant surgery (B001).

3.3 Array development: Connector technology has severely limited the number of electrodes we able to use address for recording. The generally available connector from Bionics (BTI) was a 12 pin Microtek, which allowed only connection to only 11 electrodes of the 100 available in the array. To increase recording to 22 we used two of these connectors. Subsequently we adopted a Winchester 50 pin connector, which was abandoned because of infections that developed easily under the connectors, largely as a result of its poor mating to the skull BTI developed a new generation of 45 pin connectors, called the Tulip connector, which is based on an card edge. With two of these connectors we can achieve 74 connections (with two references).We tested three of these connectors during this project period.

3.4 Array Testing

Impedance High impedances have the advantage of providing high signal to noise ratio, but the tip must be close to a neuron to obtain recordings. On the other hand, a low impedance electrode detects many cells, making it difficult to isolate neurons from background 'hash'. The goal of this part of the project is to identify the optimal impedances for UEIA. No evaluations have been made yet in the project.

Recording Stability: The ability to maintain the same cells each day of recording by the UA is not known and is important in the design of a prosthetic device. No work on this goal was performed during this period.

Tethering Forces It is believed that the wire bundle from the UIEA array to the connector provided significant tethering forces, causing the electrode to move and, hence, damage the cortex. To test the tethering hypothesis we implanted an array with 74 wires attached. Preliminary data suggests that recordings can be obtained from arrays with this may wires attached.

3.5 Histological analyses*:* The goal of histological analysis is to determine tissue reaction to the UIEA. We test for cell loss and reaction using both thionin cell stain and GFAP, to test for glial reactivity. During this quarter we carried out qualitative examination of tissue from B164. This analysis indicates that there is minimal tissue effects of the array over time. Several months after implantation there is little glial reaction, as measured by GFAP reaction product. Long term biocompatibility is also demonstrated by the ability to record neurons for years on these arrays. By qualitative measures these neurons appear to be no different in their properties from those recorded in acute preparations. Two monkeys with arrays were perfused during this project period (B-132 and b164). Tissue blocks were sent for histological processing by the pathology department at Brown University.

3.6 Recoding Technology Development. We are working with Dr. Richard Normann's group at the University of Utah to modify one of the BTI 100 channel recording/acquisition systems so that it can classify spikes in real time and provide output to a second computer. A second computer is used to decode the spike patterns, both to build movement classification models and for online classification. Working with Richard Normann and BTI we are modifying the current BTI spike acquisition device so that it is capable of providing 'spike times' in real time to the decoding computer. However, it appears that this modification will be limited to sending multi and not discriminated single unit data. Consequently, we purchased a Plexon data acquisition system for tests of real time spike control because it already has real time, sorted spike capability and it overcomes certain limitations of the BTI. Plexon is able to set up more rapidly for online classification, and most importantly only the Plexon can provide discriminated spike events to another computer in real time. Further advantages of the Plexon is that is has a higher sampling rate for more accurate spike discrimination.

4. NEURAL DECODING

The goal of this aspect of the project is to determine whether we can recover a reliable hand trajectory signal using the activity of multiple MI neurons. Our main emphasis has been on linear reconstruction methods, but we are planning to test new methods to develop better and more rapid trajectory reconstructions. Previous work has shown that neural discharge in motor cortex is related to a number of kinematic variables, including direction, position, acceleration and velocity (Georgopoulos and Ashe, 1994; Fu et al., 1993). However, these analyses have been restricted to simple evaluations of discrete, usually scalar, variables studied in tasks in which monkeys must only move from a single point to one of a few static targets; We term this a discrete (as opposed to a continuous tracking task). Because of technical limitations, cells in these earlier studies were recorded one at a time. Information underlying cortical movement control contained in the mutual activity of populations of neurons is not available from the available single electrode data; extraction of this information requires observation of not one, but many simultaneously recorded neurons. Further, just as the visual or auditory processing can not be described by single discrete parameters, the rich structure and fluidity of natural movements can not be captured by specifying, for example, average direction of hand motion over hundreds of milliseconds. Neural control of movement proceeds continuously, and satisfactory description of natural movements requires simultaneous knowledge of multiple time-varying parameters; we term tasks that require continuous movement under visually guided or internal control as *continuous tasks*. We are attempting to provide a complete description of the kinematic variables available from cortical populations, with the goal of reconstructing these continuous movements from neural data in real time.

.**4.1 Linear Decoding:** The basic approach used is one of linear reconstruction methods developed by Bialek and colleagues (see Rieke et al., 1997) which have been applied successfully to similar problems in the sensory domain. These methods are based on the classical techniques of Wiener and Kalman filtering and are simple and potentially fast enough to be easily implemented in real time, once spikes from neurons have been acquired and we have learned enough about the coding of the relevant variables in motor cortex. These techniques are designed explicitly for efficient decoding of continuously varying signals, such as a hand movement in space. Most importantly, they tell us how much of the hand trajectory can be reconstructed from a neural population. Using this approach, we can

account for up to ~70% of the variance in x or y position over time. In addition, many of the errors made in the reconstruction are in the higher frequencies; these can be easily filtered out if they are to be used as a control signal. The power of this method is that it can reconstruct any random new trajectory based on a relatively simple model. The quality of reconstructions can sometimes be significantly worse for reasons that are not yet clear. Methods to understand how to sample data to build an optimal reconstruction model are underway. In addition we have found that the same linear filter may generally applied day to day, even if the exact composition of neurons changes in the recorded population. Further, we have found that brief periods of recording, on the order of four minutes, provide sufficient data to create decoding models for accurate reconstruction of hand position. Our regression method is particularly powerful because it can recreate both position and velocity, which is an advance over traditional velocity vector reconstruction methods that have been applied in motor decoding. These findings indicate that signals indicating desired hand position can be obtained for long periods from motor cortex.

Linear, LMS filtering These methods use a standard least mean squares signal reconstruction algorithm, similar in some respects to classical Wiener filtering of signals buried in noise. In this approach, a causal filter is associated to the firing rate of each cell, and the movement signal is reconstructed by convolving, in turn, the spike train from each neuron with the associated filter and then summing the resulting signals together. In symbolic form, the reconstructed movement signal is simply

$$M_R(t) = \sum_{i=1}^{n} N_i(t) * F_i(t),$$

where $M_R(t)$ is the reconstructed movement signal, $N_i(t)$ is the spike train (spikes/time) from neuron i, $F_i(t)$ is the filter corresponding to neuron i, * denotes convolution, and n is the number of neurons from which we are recording. The filters F_i are chosen such that the

$$E_{ms} = \int (M_R(t) - M(t))^2 dt$$

mean-squared error between the reconstructed movement and the actual movement,

with M(t) denoting the true movement, is minimized. All of these equations are, of course, in discrete time. The signals M(t) and $M_R(t)$, and the filters F_I, are in fact two-dimensional functions of time, corresponding to x- and y-position through time.) The algorithm for finding the optimal filters F_i requires the inversion of a correlation matrix, which can be efficiently implemented via the Durbin recursion; it is clear that, after the filters are found, the reconstruction algorithm is exceedingly simple, and can potentially be implemented in real time.

4.2 Nonparametric decoding The major strength and weakness of the approach outlined above is its simplicity: linear filtering is fast and easy, but fails as the complexity of the encoding of the relevant signals increases. It still remains unclear what the full spectrum of information is for motor cortex. As emphasized above, in the description of the continuous tracking task, we know very little about the detailed encoding of variables in MI, and we might not be able to rely on linear decoding algorithms to extract the information we need for this project. Thus, we turn to a decoding method that makes fewer assumptions about neural coding in MI, which can be termed "Bayesian reconstruction." In this approach, we associate with each neuron (or, in the more general setting introduced above, each "neural

event") a probability distribution (p.d.f.) on the space of possible movements in the time immediately surrounding the neural event given that specific neural event, $P_i \equiv P(movement \mid event = i)$. We also gather information on the *a priori* probability of movements and of occurrences of neural events (i.e., estimate the prior, or marginal, distributions on these signals). Using Bayes' law, we can compute the probability of a forthcoming movement at a given time t, given that we know the available neural information up to t (represented as events i), the prior distribution on movements, and the prior distribution on the occurrences of neural events. We then choose the path that corresponds to the mean of this conditional distribution as our reconstruction. If we have adequately characterized the joint p.d.f. on movements and neural signals (clearly a very strong condition, but one whose validity may be examined using a simple information-theoretic analysis), this conditional mean reconstruction strategy is optimal in the mean-square sense, under no assumptions on the linearity or noise distribution of encoding. In reality, we have to make some key assumptions about independence of variables in the space of neural and movement signals (discussed further below) in order to implement this decoding algorithm, and we can not guarantee L^2 optimality, but we can hope these assumptions do not perturb our solution too far away from the optimum. Real-time implementation of this algorithm follows the outline above and is straightforward under these independence assumptions. The Bayesian approach and the linear decoding approach are comparably computationally intensive; however, the Bayesian algorithm, due to its greater flexibility, requires much more training data for adequate signal reconstruction when the signal happens to be linearly encoded.

Error: The suitability of decoding is measured by various error measures. We use the correlation coefficient between the actual movement and the reconstructed one. We also apply analyses in the spectral domain. (from which standard measures of reconstruction quality such as E_{ms} or transformation are easily derived) of varying the parameters involved in the reconstructing algorithms. These parameters include: the length in time of the linear filters F_i, the length in time of the neural event-conditional probability distributions P_i (or, more properly, the dimension of the space on which these distributions reside), the resolution of the time-discretization of the filters and signals involved, the number of cells involved, the quality of the isolation of single-unit activity, the amount of training data used, the different degrees of probabilistic independence (between cells, between time steps, etc.) assumed to be present in the cellular activity we record, etc.

4.3 Other Issues

We are planning to develop statistical learning and probabilistic inference techniques are used to infer arm position from multi-electrode recordings. For these models we will use non-parametric representations of firing activity using a Bayesian approach and compare it with previous models using cross-validation.

5. Interface development

The goals of this aspect of the project are (5.1) to develop interfaces with peripheral devices (i.e., robot arm, computer), (5.2) demonstrate that decoded neural signals can be used to control such peripheral devices, and (5.3) demonstrate that monkeys can bring this signal under near real time control.

5.1 Interface with peripheral devices We acquired a CRS robot arm and determined how to generate control signals to the command hardware.

5.2 Offline control of prosthetic devices*:* No work was completed on this aspect of the project during the present project period.

5.3 Real time Control of prosthetic devices: No work was completed on this aspect of the project during the present project period.

5.4 Arm paralysis/Control without feedback. The goal is to demonstrate that monkeys are able to control the robot arm using neural activity when arm actions are impossible and sensory feedback is missing, a condition that mimics human paralysis. This will be achieved by blocking the brachial plexus with injection of sodium channel blockers (lidocaine, Klein et al., 1998). This procedure can be used reversibly to eliminate all movement and sensation from the arm for a period of hours. The method is used safely and repeatedly in humans for surgical procedures as well as chronically (Lierz et al., 1998), so it represents minimal risk to the health or well being of the monkey. It is a reasonable substitute for arm amputation which is a more invasive way to demonstrate that motor cortical neural activity can be used for control when the effector member is missing. For testing, a monkey trained to position a computer cursor in our tracking tasks will receive a brachial plexus blockade. Then the monkey will be presented with the visual display and feedback. Cursor position will be controlled using the neural output, based upon a set of linear filters built from task performance immediately before arm paralysis. No work was completed on this aspect of the project during the present project period.

6.0 Plans For Next Quarter

1 Array Development

- **Behavioral Training:** There are currently 7 contract monkeys being trained for implantation and array testing.
- **Button box task** Button boxes software will be completed and a new computer interface will be completed that will allow control of cage trainers by one computer. Three monkeys will be trained to perform the radial task using this apparatus. We will make improvements in the button box software and make alterations in the hardware to increase the number of button boxes running at the same. Three monkeys will continue being trained to perform the radial task using this apparatus, and two more monkeys will begin training for the first time. Two monkeys will continue chair training with the button box for recording purposes.
- **Radial task & Continuous tracking.** Two monkeys are continuing to train in these tasks for recording purposes, 5 additional monkeys are being trained in these tasks for future implantations.
- **Arrays/implantation & Surgical Procedures** One implantation is planned for a tulip array, to be used for decoding and interface studies. We are scheduling several array implantation surgeries in anticipation of delivery of a new 100 pin connector (expected 9/21/01) from BTI which will allow us to record from all 100 electrodes; in addition this connector appears to have a number of other features (such as a low profile and durability) which will make it much more suitable as a long term implant.

- **Array development.** In the next quarter we plan to test further tulip arrays and to test the tethering problem using arrays with large numbers of wires
- **Array testing** We will continue to recording s from all monkeys with viable recordings. These will provide data for the neural decoding and stability analyses.
- **Histology** We will examine processed tissue from two monkeys that were perfused before this contract began. It is anticipated that histological processing will begin on at least on additional monkey.
- **Neural Decoding**

  a. Linear Reconstruction; We will test the day to day stability of linear decoders by using filters established on one day for the next days data set.

  b. Other methods; Drs. Bienenstock and Black will continue to evaluate methods that use probabilistic inference to decode neural activity, as described in our NIPS manuscript

3. **Interface Development**

   a. Peripheral devices interfaces. Mr. Shakouni will complete and improve software to drive the robot arm and allow it to accept input from the decoding spike trains.

   b. Offline control We will begin to test the ability to drive both the robot arm and a PC cursor via already recorded neural data that is decoded using a Lab View Interface**.**

   c. Real Time control. Mr. Serruya will begin to evaluate the ability for monkeys to control a position feedback cursor for a behavioral task.

   d. Arm paralysis/control without feedback. We will test direct injection methods to achieve arm paralysis. Dr. Emory Brown of Harvard Medical School, will provide assistance us in implementing methods that allow us to safely inject local anesthetic into the brachial plexus.